histiocytosis-lymphadenopathy plus syndrome

Histiocytosis-lymphadenopathy plus syndrome (also known as *SLC29A3* spectrum disorder) is a group of conditions with overlapping signs and symptoms that affect many parts of the body. This group of disorders includes H syndrome, pigmented hypertrichosis with insulin-dependent diabetes mellitus (PHID), Faisalabad histiocytosis, and familial Rosai-Dorfman disease (also known as sinus histiocytosis with massive lymphadenopathy or SHML). These conditions were once thought to be distinct disorders; however, because of the overlapping features and shared genetic cause, they are now considered to be part of the same disease spectrum. While some affected individuals have signs and symptoms characteristic of one of the conditions, others have a range of features from two or more of the conditions. The pattern of signs and symptoms can vary even within the same family.

A feature common to the disorders in this spectrum is histiocytosis, which is the overgrowth of immune system cells called histiocytes. The cells abnormally accumulate in one or more tissues in the body, which can lead to organ or tissue damage. The buildup often occurs in the lymph nodes, leading to swelling of the lymph nodes (lymphadenopathy). Other areas of cell accumulation can include the skin, kidneys, brain and spinal cord (central nervous system), or digestive tract.

This spectrum is known as histiocytosis-lymphadenopathy plus syndrome because the disorders that make up the spectrum can have additional signs and symptoms. A characteristic feature of H syndrome is abnormal patches of skin (lesions), typically on the lower body. These lesions are unusually dark (hyperpigmented) and have excessive hair growth (hypertrichosis). In addition, histiocytes accumulate at the site of the skin lesions. Other features of H syndrome include enlargement of the liver (hepatomegaly), heart abnormalities, hearing loss, reduced amounts of hormones that direct sexual development (hypogonadism), and short stature.

Like H syndrome, PHID causes patches of hyperpigmented skin with hypertrichosis. PHID is also characterized by the development of type 1 diabetes (also known as insulin-dependent diabetes mellitus), which usually begins in childhood. Type 1 diabetes occurs when the body does not produce enough of the hormone insulin, leading to dysregulation of blood sugar levels.

Faisalabad histiocytosis typically causes lymphadenopathy and swelling of the eyelids due to accumulation of histiocytes. Affected individuals can also have joint deformities called contractures in their fingers or toes and hearing loss.

The most common feature of familial Rosai-Dorfman disease is lymphadenopathy, usually affecting lymph nodes in the neck. Histiocytes can also accumulate in other parts of the body.

Frequency

Histiocytosis-lymphadenopathy plus syndrome is a rare disorder, affecting approximately 100 individuals worldwide.

Genetic Changes

Histiocytosis-lymphadenopathy plus syndrome is caused by mutations in the *SLC29A3* gene, which provides instructions for making a protein called equilibrative nucleoside transporter 3 (ENT3). ENT3 belongs to a family of proteins that transport molecules called nucleosides in cells. With chemical modification, nucleosides become the building blocks of DNA, its chemical cousin RNA, and molecules such as ATP and GTP, which serve as energy sources in the cell. Molecules derived from nucleosides play an important role in many functions throughout the body.

ENT3 is found in cellular structures called lysosomes, which break down large molecules into smaller ones that can be reused by cells. Researchers believe that this protein transports nucleosides generated by the breakdown of DNA and RNA out of lysosomes into the cell so they can be reused. The protein is also thought to transport nucleosides into structures called mitochondria, which are the energy-producing centers of cells. In mitochondria, nucleosides are likely used in the formation or repair of DNA found in these structures, known as mitochondrial DNA.

The *SLC29A3* gene mutations involved in histiocytosis-lymphadenopathy plus syndrome reduce or eliminate the activity of the ENT3 protein. Researchers speculate that the resulting impairment of nucleoside transport leads to a buildup of nucleosides in lysosomes, which may be damaging to cell function. A lack of ENT3 activity may also lead to a reduction in the amount of nucleosides in mitochondria. This nucleoside shortage could impair cellular energy production, which would impact many body systems. It is unclear how the mutations lead to histiocytosis and other features of the condition or why affected individuals can have different patterns of signs and symptoms.

Inheritance Pattern

This condition is inherited in an autosomal recessive pattern, which means both copies of the gene in each cell have mutations. The parents of an individual with an autosomal recessive condition each carry one copy of the mutated gene, but they typically do not show signs and symptoms of the condition.

Other Names for This Condition

- SLC29A3 disorder
- SLC29A3 spectrum disorder

Diagnosis & Management

Genetic Testing

- Genetic Testing Registry: Histiocytosis-lymphadenopathy plus syndrome
  https://www.ncbi.nlm.nih.gov/gtr/conditions/C1864445/

General Information from MedlinePlus

- Diagnostic Tests
  https://medlineplus.gov/diagnostictests.html
- Drug Therapy
  https://medlineplus.gov/drugtherapy.html
- Genetic Counseling
  https://medlineplus.gov/geneticcounseling.html
- Palliative Care
  https://medlineplus.gov/palliativecare.html
- Surgery and Rehabilitation
  https://medlineplus.gov/surgeryandrehabilitation.html

Additional Information & Resources

MedlinePlus

- Encyclopedia: Histiocyte
  https://medlineplus.gov/ency/article/002374.htm
- Encyclopedia: Type 1 Diabetes
  https://medlineplus.gov/ency/article/000305.htm
- Health Topic: Lymphatic Diseases
  https://medlineplus.gov/lymphaticdiseases.html
- Health Topic: Skin Pigmentation Disorders
  https://medlineplus.gov/skinpigmentationdisorders.html

Genetic and Rare Diseases Information Center

- Histiocytosis-lymphadenopathy plus syndrome
  https://rarediseases.info.nih.gov/diseases/10239/histiocytosis-lymphadenopathy-plus-syndrome
- Rosai-Dorfman disease
  https://rarediseases.info.nih.gov/diseases/7588/rosai-dorfman-disease

Educational Resources

- MalaCards: histiocytosis-lymphadenopathy plus syndrome
  http://www.malacards.org/card/histiocytosis_lymphadenopathy_plus_syndrome
- Merck Manual Home Health Handbook: Overview of Skin Pigment
  http://www.merckmanuals.com/home/skin-disorders/pigment-disorders/overview-of-skin-pigment
- Merck Manual Professional Edition: Overview of Histiocytic Syndromes
  http://www.merckmanuals.com/professional/hematology-and-oncology/histiocytic-syndromes/overview-of-histiocytic-syndromes
- Orphanet: H syndrome
  http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=168569
- Orphanet: Rosaï-Dorfman disease
  http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=158014
- University of Rochester Medical Center: Lymphadenopathy
  https://www.urmc.rochester.edu/encyclopedia/content.aspx?ContentTypeID=90&ContentID=P02044

Patient Support and Advocacy Resources

- American Diabetes Association
  http://www.diabetes.org/diabetes-basics/type-1/
- American Skin Association
  http://www.americanskin.org/
- Histiocytosis Association: Rosai-Dorfman Disease
  http://www.histio.org/page.aspx?pid=399#.VIhronvxidx

Scientific Articles on PubMed

- PubMed
  https://www.ncbi.nlm.nih.gov/pubmed?term=%28%28histiocytosis-lymphadenopathy+plus+syndrome%5BTIAB%5D%29+OR+%28H+syndrome%5BTIAB%5D%29+OR+%28Faisalabad+histiocytosis%5BTIAB%5D%29+OR+%28familial+Rosai-Dorfman+disease%5BTIAB%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+3600+days%22%5Bdp%5D

OMIM

- HISTIOCYTOSIS-LYMPHADENOPATHY PLUS SYNDROME
  http://omim.org/entry/602782

Sources for This Summary

- Bolze A, Abhyankar A, Grant AV, Patel B, Yadav R, Byun M, Caillez D, Emile JF, Pastor-Anglada M, Abel L, Puel A, Govindarajan R, de Pontual L, Casanova JL. A mild form of SLC29A3 disorder: a frameshift deletion leads to the paradoxical translation of an otherwise noncoding mRNA splice variant. PLoS One. 2012;7(1):e29708. doi: 10.1371/journal.pone.0029708. Epub 2012 Jan 4.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/22238637
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3251605/
- Kang N, Jun AH, Bhutia YD, Kannan N, Unadkat JD, Govindarajan R. Human equilibrative nucleoside transporter-3 (hENT3) spectrum disorder mutations impair nucleoside transport, protein localization, and stability. J Biol Chem. 2010 Sep 3;285(36):28343-52. doi: 10.1074/jbc.M110.109199. Epub 2010 Jul 1.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/20595384
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2934698/
- Morgan NV, Morris MR, Cangul H, Gleeson D, Straatman-Iwanowska A, Davies N, Keenan S, Pasha S, Rahman F, Gentle D, Vreeswijk MP, Devilee P, Knowles MA, Ceylaner S, Trembath RC, Dalence C, Kismet E, Köseoglu V, Rossbach HC, Gissen P, Tannahill D, Maher ER. Mutations in SLC29A3, encoding an equilibrative nucleoside transporter ENT3, cause a familial histiocytosis syndrome (Faisalabad histiocytosis) and familial Rosai-Dorfman disease. PLoS Genet. 2010 Feb 5;6(2):e1000833. doi: 10.1371/journal.pgen.1000833.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/20140240
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2816679/
- Spiegel R, Cliffe ST, Buckley MF, Crow YJ, Urquhart J, Horovitz Y, Tenenbaum-Rakover Y, Newman WG, Donnai D, Shalev SA. Expanding the clinical spectrum of SLC29A3 gene defects. Eur J Med Genet. 2010 Sep-Oct;53(5):309-13. doi: 10.1016/j.ejmg.2010.06.012. Epub 2010 Jul 7.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/20619369

Reprinted from Genetics Home Reference:
https://ghr.nlm.nih.gov/condition/histiocytosis-lymphadenopathy-plus-syndrome

Reviewed: December 2014
Published: March 21, 2017

Lister Hill National Center for Biomedical Communications
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National Institutes of Health
Department of Health & Human Services